

A Ten-Year Study of Anencephaly

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ETIOLOGIC STUDIES of anencephalic births have not been conclusive enough to establish whether the phenomenon is attributable to genetic or to environmental factors and no single theory has received wide acceptance.

Ingalls¹⁶ emphasized the need for further statistical reports. He suggested that first the incidence of congenital anomalies in a community be determined; then a combined medical interdisciplinary effort could have basis for evaluation of corrective measures taken to reduce the incidence of such abnormalities.

Further investigation into the nature of congenital anomalies such as anencephaly may offer clarification of the genetic implications of the incidence of abortion and malformation.

To this end an analysis was made of the cases of anencephaly at the Los Angeles County General Hospital during the period July, 1948, through June, 1958.

There were 48 anencephalic births in 97,381 deliveries at the Los Angeles County General Hospital during the ten-year period of this study, an incidence of 0.049 per cent. Penrose,²³ in a survey of the world literature, noted a range from 0.012 per cent to 0.671 per cent. The broad incidence range apparently has some relationship to the geographical area in which the study of anencephaly is made.

The *British Medical Journal*,⁷ in an editorial review, reported that in Belfast and Dublin the incidence is 0.671 per cent and 0.502 per cent respectively. The reported rate in these two cities is three times greater than in Birmingham, England, and fifty times greater than in Lyons, France. In the United States the incidence in various studies has ranged from 0.057 per cent to 0.231 per cent (Table 1).

Sex Ratio

In the present study the females numbered 65 per cent of the total. As noted by MacMahon and McKeown,¹⁷ the proportion of males increased with the length of gestation. In this study 69 per cent of the 35 anencephalics born prematurely were females while only 54 per cent of the 13 anencephalics born at term were females. No satisfactory

• The incidence of anencephaly at the Los Angeles County General Hospital during the period of July, 1948 through June, 1958 was 0.049 per cent. Worldwide the range of reported incidence is 0.012 per cent to 0.671 per cent.

In this study 65 per cent of the total number of anencephalics delivered were females, a predominance agreeing with reports by other investigators.

Polyhydramnios appeared in 38 per cent of the anencephalic pregnancies of this study, while 15 per cent of the deliveries were complicated by placenta praevia.

A significant number (48 per cent) of the multiparae gave a history of previous stillbirths or abortions.

The present study does not support observations by other investigators which indicated an increase in anencephalic births during the winter months.

Evidence from stillbirth statistics would seem to indicate that anencephaly is primarily a genetically induced phenomenon. Further evaluation and analysis of the predominance of females in anencephalic stillbirths and abortions is suggested, in order to study whether the observed secondary or birth sex ratio (in which males predominate) is, in fact, due to genetic effect.

explanation has yet been put forward⁷ for the higher incidence in females, the range being from 57 per cent to 87 per cent in various reports.¹³

The question of whether examination of the external genitalia gives a valid indication of the true sex of the anencephalic was raised by Perrin and Benirschke.²⁴ They reviewed slides of 35 anencephalic fetuses to compare the results of nuclear or somatic sex with that of the observed external sexual characteristics. They reported that the "nuclear sex" was in accord with the sex as recorded by external examination, and that in the review of sections of gonads no hermaphrodite abnormalities were noted.

In 1959 Bearn¹ investigated the relationship of the nuclear chromatin of anencephalics to their phenotype. He indicated that the predominance of females may be related to sex reversal with failure of masculinization of the genital tract. This initial hypothesis was related to the reports that the small adrenal gland of the anencephalic was due to an abnormal pituitary gland. Pituitary and adrenal hypoplasia are found consistently in anencephaly.

From the Los Angeles County General Hospital, Los Angeles 33.
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TABLE 1.—Incidence of Anencephalus in the United States

Area, Author and Year Reported	Period	No. Births	No. Anencephalics	Per Cent of Total
Rhode Island, MacMahon, et al., 1953	1936-52	168,654	326	0.193
Rochester, Minn., Harris & Steinberg, 1954	1944-50	8,716	5	0.057
Fall River, Mass., Hurwitz, 1955	1948-54	5,264	15	0.280
Wilmington, Del., Monahan, 1956	1954-55	12,529	11	0.087
Boston, Mass., Stevenson, et al. (Böök and Francaro, 1956)	1930-41	29,024	67	0.231
New York, New York, Marcus & Brandt, 1957	1948-57	11,946	26	0.22
Los Angeles, Calif., Smilkstein, 1958	1948-58	97,381	48	0.049

However, Bearn's investigation of 24 anencephalic fetuses demonstrated that the 21 chromatin-positive fetuses had normal female external genitalia and that the 3 chromatin-negative fetuses had normal male external genitalia.

Race

The data from the Los Angeles County General Hospital are of special interest since this hospital serves basically three racial groups: Caucasian, Mexican-Caucasian, and Negro. The total number of anencephalic births was divided 15, 15 and 18 respectively (Table 2). When correlated with the total number of deliveries by each racial group, these figures would suggest that the incidence of anencephaly is not necessarily equal; for Caucasians make up 24.1 per cent of the total deliveries, Mexican-Caucasians 30.7 per cent and Negroes 44.0 per cent. In all cases in this series the fathers were of the same race as the mothers.

Polyhydramnios and Placenta Praevia

In this series, 38 per cent (18) of the pregnancies were associated with polyhydramnios and 15 per cent (7) were complicated by placenta praevia. It would appear that polyhydramnios is one of the most common associated factors of the anencephalic pregnancy. Reported incidence of polyhydramnios varies from 50 to 69 per cent.¹³ The incidence of placenta praevia in this series was 15 times as common as in the general population.²

Previous Abortions and Stillbirths

A total of 16 abortions and 11 stillbirths were previously experienced by the mothers of anencephalic offspring. Forty-eight per cent of 35 multiparae gave a history of previous stillbirths or abortion or both. Similar observations have been made by Böök and Rayner,³ and Record and McKeown.²⁵

In Coffey and Jessop's⁵ series of 137 cases of anencephaly, 26 of the 98 multiparae had previously given birth to a congenitally abnormal baby. Seven of the multiparae had delivered anencephalics. In a second study reported in 1958, Coffey and Jessop⁶ reported that 9 of 122 had previous anencephalic births.

TABLE 2.—Frequency of Anencephaly According to Race, Age of Mother and Order of Birth of Infant

Caucasian	15
Caucasian-Mexican	15
Negro	18
Mother's age (years):	
19 and under	9
20 to 24	18
25 to 29	12
30 to 34	5
35 and over	4
Order of birth:	
First	13
Second or third	14
Fourth to sixth	13
Seventh or beyond	8

TABLE 3.—Seasonal Variation in Anencephalic Births

Seasons	Anencephalic Births
November, December, January, February	15
March, April, May, June	18
July, August, September, October	15

Associated Anomalies

In 35 per cent of the anencephalics, associated congenital anomalies were reported. Central nervous system abnormality was present in 11 cases, in 3 of which it was spina bifida.

Anomalies reported were rachischisis totalis, Arnold Chiari syndrome, meningomyelocele, encephalomeningocele, cyclopia, agenesis left eye, hydroureter, horseshoe kidney, hypoplasia right kidney, Eisenmenger's complex, club foot, cleft palate, hare lip and syndactyly.

Seasonal Variation

The seasonal variation as reported by McKeown and Record²¹ and Edwards⁸ is not supported by this study (Table 3). Their studies done in the British Isles indicated that stillbirth rates attributable to anencephaly were approximately 50 per cent greater in winter months than in the summer. In the present study an almost equal distribution through the year was noted. While it might be suspected that the rather uniform climate in Southern California accounts for the absence of a seasonal variation in the birth rate, MacMahon and

coworkers¹⁸ were unable to find a seasonal influence in the incidence of anencephalics in a Rhode Island series.

DISCUSSION

The etiology of anencephaly is a most challenging problem. Coffey and Jessop⁶ pointed out the many difficulties in the establishment of a genetic and/or environmental basis for anencephaly.

Ingalls,¹⁴ Hicks¹² and Evans and coworkers⁹ showed that by the exposure of the experimental animal to adverse environmental situations such as anoxia, ionizing radiation and vitamin deficiency, central nervous system anomalies, including anencephaly, can be produced. However, statistical checks to investigate a possible relationship between environmental stresses and the incidence of anencephaly in humans have proven inconclusive in the following areas: Attempted abortions, war years, malnutrition, chemical poisons, alcohol, tobacco, food preservatives, hormones and mechanical trauma (Edwards,⁸ Penrose²³ and Coffey and Jessop⁵).

Anencephaly has been reported in one of a pair of uniovular twins.²⁶ In this instance the action of an environmental factor should be considered either alone or as influencing the hereditary constitution of one twin.

Environmental factors, such as illness during first trimester, previous medical illness and abnormal menstrual history, appeared infrequently in patients' histories in the Los Angeles County General Hospital study. With regard to environmental factors, Coffey and Jessop⁵ reported that in their study of 137 cases of anencephaly they noted no significant difference from their controls.

A higher incidence of anencephaly in children of parents in older age groups was early reported by Malpas.¹⁹ However, the present study does not support such a finding (Table 2). Record and McKeown²⁵ and Böök and Rayner³ considered age of the mother of little bearing, whereas an association with order of birth seemed to be of some significance.

Edwards,⁸ in an extensive study of congenital malformations of the central nervous system in Scotland, noted that "improved social conditions which have led to a great reduction in most other causes of stillbirths, have not influenced the year to year rate of anencephalic births."

In 1936 Bonnevie³ demonstrated a lethal recessive gene in mice, termed *pseudencephaly*, which results, in most cases, in a major disturbance which causes death of an embryo followed by absorption in utero or abortion.

The abortion rate in mothers who bore an anencephalic child was 37 per cent in the present study. It was reported at 20 per cent by Böök and

Rayner.³ Hertig¹¹ in 1954 reported that the abortion rate of anomalous fetuses is about four times the incidence of anomalous children born either alive or dead.

In a study of 181,548 stillbirths, Ciocco⁴ found the total male stillbirths to be 103,642, and the total female stillbirths, 77,906. When Ciocco divided the total stillbirths into subgroups according to the cause of death, in only one category, malformations, were there more female stillbirths than male. Of 10,301 stillbirths due to malformations, the ratio was 748.9 males to 1,000 females. It is of interest that in the other categories for causes of stillbirths, such as maternal disease, fetal injury and anomalies of the placenta and cord, in which environmental factor rather than genetic disease would be the primary consideration, the stillbirth sex ratio showed a predominance of males.

A question that might be considered is whether the sex ratio of anencephaly in humans, which shows a predominance of females, can be explained on other than a genetic basis. It is of interest that in the report of Ingalls and coworkers,¹⁵ in which pregnant white mice were exposed to varying degrees of oxygen lack, the offspring of the test mice in which congenital anomalies were produced showed essentially the same sex ratio as the offspring of the control group. This point is raised since it seems plausible to hypothesize that when a noxious agent is introduced in the postfertilization stage both sexes should be affected equally; however, when an effect makes itself known by altering the somatic structure of primarily one sex, a prefertilization or genetic mechanism should be suspected.

Further genetic studies may be indicated to evaluate the effect of loss of embryos through *in utero* absorption and abortion, in which females outnumber males (as is the case in anencephaly). Such studies may help to explain the observed secondary sex ratio in the general population in which males outnumber females.

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